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Review

Staging and grading of oral squamous cell carcinoma: An update

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ABSTRACT

Oral squamous cell carcinoma (OSCC) is a common malignancy of the head and neck region. OSCC has a relatively low survival rate and the incidence of the disease is increasing in some geographic areas. Staging and grading of OSCC are established prerequisites for management, as they influence risk stratification and are the first step toward personalized treatment. The current AJCC/UICC TNM staging (8th edition, 2017) of OSCC has included significant modifications through the incorporation of depth of invasion in the T stage and extracapsular spread/extranodal extension in the N stage. Further modifications for AJCC 8 have been suggested. On the other hand, the World Health Organization (WHO) classification (4th edition, 2017) still endorses a simple, differentiation-based histopathologic grading system of OSCC (despite its low prognostic value) and ignores factors such as tumor growth pattern and dissociation, stromal reactions (desmoplasia, local immune response), and tumor-stroma ratio. The various controversies and possible developments of the current staging and grading criteria of OSCC are briefly discussed in this update together with possible applications of artificial intelligence in the context of screening and risk stratification.

Introduction

Oral cancer is a significant health problem and regarded as the main cause of death from oral diseases in many countries. Recent global estimates have revealed 354,864 new cases and 177,384 deaths in 2018 [1]. Traditional risk factors of oral cancer include tobacco and alcohol abuse. Conventional oral squamous cell carcinoma (OSCC) is one of the

most common cancers of the head and neck; the incidence of OSCC has increased in many countries, especially in younger age groups [2,3]. Whether or not young and old patients with OSCC have a different prognosis remains a controversial issue [4,5]. However, no significant differences were observed in the tumor stage or grade in recent studies that compared the characteristics of OSCC in young and old patients [4,6,7]. The oral tongue is the most common subsite and is associated

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with higher mortality than OSCC in other subsites (e.g. floor of mouth, gingivae, and retromolar trigone) according to a recent analysis of Surveillance, Epidemiology, and End Results (SEER) database [8].

Management of OSCC is based on surgical resection with or without adjuvant treatment (e.g. radiotherapy or chemoradiotherapy). The indication for adjuvant treatment is influenced by features detailed in the standardized histopathology report of the resection, which include differentiation, growth pattern, depth of invasion, status of margins, vascular/neural invasion, bone involvement, nodal status (number of lymph nodes involved, size of largest metastasis, extracapsular spread (ECS)/extranodal extension (ENE)), and pTNM staging. Standardized histopathological reporting has been pioneered by the minimum data sets issued by the Royal College of Pathologists (United Kingdom) in 2005 [9]; and an international version has been published recently [10]. Because recent studies are centered on the role of immunotherapy with the use of immune checkpoint inhibitors, PDL-1 immunohistochemical staining of tumor biopsies becomes important in guiding patient selection for PD-1/PD-L1 inhibitor therapy [11].

TNM staging of OSCC

The TNM system of cancer staging reflects the extent of tumor growth in the whole body and is based on assessment of the size of the primary tumor (T), involvement of locoregional lymph nodes (N), and distant metastases (M). This classification is important for treatment planning, estimating risk of recurrence, and assessment of overall survival. However, this classification only considers the anatomic extension of the disease and not the other prognostic factors, such as comorbidity or treatment [12].

The International Union Against Cancer (UICC) published the first edition of the TNM staging in 1968, whereas the American Joint Committee on Cancer (AJCC) published its first staging manual in 1977. Later editions were synchronized and effected updating. In 2017, the 8th edition of the UICC and AJCC (AJCC 8) staging manual was released [13,14]. It introduced two major changes for OSCC, namely incorporation of the tumor depth of invasion (DOI) in the T stage and incorporation of extracapsular spread (ECS) in the N stage. Several studies have examined the performance of AJCC 8 in independent cohorts of OSCC [15–18] and the need for further development is acknowledged.

DOI, also known as reconstructed tumor thickness, is different from clinical tumor thickness, particularly in exophytic and ulcerated lesions. DOI was originally envisaged as distance from a theoretical reconstructed normal mucosal surface line to the deepest extent of growth [19,20]. Recently, Müller et al. (2019) favored the level of the epithelial basement membrane zone instead of the normal mucosal surface [10], although the value of this is debatable. The AJCC 8 manual and UICC Atlas suggest that DOI can be reliably defined clinically, but DOI seems difficult to estimate by palpation only. An alternative to overcome these difficulties would be the use of preoperative imaging (e.g. magnetic resonance imaging (MRI) or ultrasound (US)) to assess the depth of invasion and tumor thickness. In a retrospective study, Dirven et al. found that the T category and the TNM stage prognostic performance of the AJCC 8 staging of oral cancer is similar regardless of whether DOI or tumor thickness was used as the T-category modifier [18].

A recent systematic review and a meta-analysis, including individual participant data of 240 patients, showed a high correlation of tumor thickness within this subgroup as measured by intraoral US and histopathology ($r = 0.82$, $P < 0.001$), with minor overestimation of 0.5 mm on US [21]. It was concluded that intraoral US is very accurate in determining tumor thickness in early oral tongue cancer [21]. This was confirmed in a more recent systematic review including 471 patients, in which a pooled correlation coefficient of 0.95 was observed [22]. Regarding preoperative imaging (CT or MRI), Weimar et al. [17] successfully used the measurements of tumor thickness as a modifier for T stage in AJCC 8; these results were corroborated by Dirven et al. [18].

Lwin et al. [23] compared radiological tumor thickness (RTT) with histological tumor thickness (HTT) for OSCC and reported that although RTT shows a somewhat predictable relationship with HTT, this varies between sub-sites with better results for tongue using axial MRI. These authors acknowledged the need for evaluating the role of biomarkers and US. In this context, Brouwer de Koning et al. [24] recently reported that tumor thickness for preoperative staging of OSCC can be more accurately measured with US than with MRI.

It has been emphasized that the modifications included in AJCC 8 have caused upstaging of many cases according to recently published studies [15,18,25]. In a recent analysis of a large cohort, Lee et al. [26] reported that upstaging has occurred in 12.4% of cases for pT stage, in 13.3% for the pN stage, and in 24.8% for the overall stage. Similarly, when DOI was incorporated for cT stage of early oral tongue cancer, upstaging was noted [15]. This would influence treatment planning, as OSCC cases that were early stage according to AJCC 7 are now upstaged as advanced lesions according to AJCC 8. In a series of 199 patients with AJCC 7 cT1-2N0 oral cancer subjected to sentinel node biopsy, a (pretreatment) clinical upstage (to T3) of 8% was found [27].

The implementation of AJCC 8 has been influenced by the multiple corrections made to the original printed edition and by the fact that the histopathological assessment of DOI in some cases is subject to uncertainty and inter-observer variability. For instance, according to the first version of AJCC 8, tumors > 4 cm or any tumor with DOI > 10 mm were considered T3. This statement contrasts with the latest version of the erratum, which defines T3 as tumors between > 2 cm and ≤ 4 cm with DOI > 10 mm or tumors > 4 cm with DOI ≤ 10 mm [28]. Therefore, it was not made clear until the third version that it is DOI *in conjunction* with tumor size that determines the T category. It is imperative to be aware of these corrections as these changes may affect the interpretation and conclusions of some clinical studies related to the performance of AJCC 8.

A suggestion has been made to lower the threshold of T stage. As an example, Almagush et al. suggested lowering the cutoff point (from 5 mm to 2 mm for T1 and from 10 mm to 4 mm for T2) to better categorize the risk groups of early oral tongue cancer cases [15]. Further, recent studies [16,29,30] have proposed considering the number of positive metastatic nodes to modify the N stage. Determining the ideal cutoff point of DOI and the number of positive nodes used as modifiers of T and N stages with adequate risk discrimination still requires further validation studies to examine these recently proposed modifications.

In an attempt to improve recognition of DOI and reconstructed thickness, Woolgar and Triantafyllou [19,20,31] used linear segments and curved lines on histopathological photomicrographs, a practice later endorsed by Lydiatt et al. [32] and Müller et al. [10]. It is observed that Lydiatt et al. [32] drew a horizontal line to the closest adjacent intact mucosa and dropped a “plumb” line perpendicular to it, but it appears that a study of the figures suffices. Obtaining slices of tissue perpendicular to the mucosal surface during macroscopical cutting is of paramount significance in establishing DOI. Such slices are often easier to obtain in segmental glossectomies, including the curvature of the lateral border of the tongue. Purported cases where DOI can be underestimated or overestimated include absence of adjacent intact mucosa, absence or only minimal residual tumor after biopsy, extra-tumoral perineural or vascular invasion, and a positive deep margin [33]. However, the absence of adjacent mucosa seems unlikely in resections. In cases of a positive deep margin, the pathologist should measure and report what has been available (resections are likely > 5.0 mm thick); hence, the tumor would be of an adversely prognostic thickness and precise measurement would not influence clinical decisions. More challenging is the case of perineural invasion. If “satellites” are present ahead of the main front, the sensible action would possibly be to measure the DOI of the mass and also to include in the pathology report the distance of the perineural invasion from the main tumor front (Fig. 1) [34]. If the tumor shows a dispersed growth

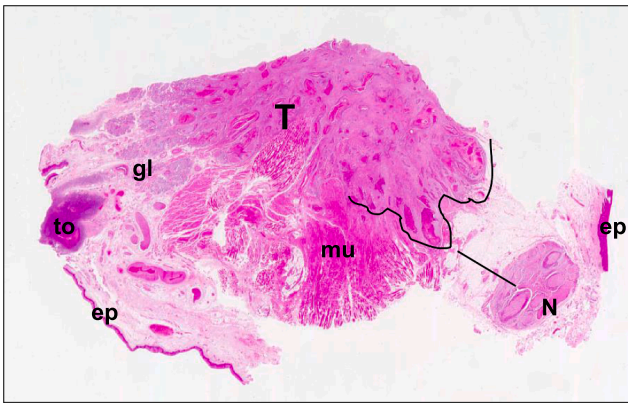


Fig. 1. SCC invades nerve fascicles ahead of its main front. Key: e, surface, epithelial; gl, glands; mu, muscle; N, nerves; T, tumor; to, tonsil. The curved line indicates the main front. The distance between invaded nerves and main front (straight line) should be measured (H & E). Modified from Woolgar JA, Triantafyllou A. A histopathological appraisal of surgical margins in oral and oropharyngeal cancer resection specimens. *Oral Oncol.* 41:1034-43, 2005.

pattern and perineural invasion [10], it would seem sensible to regard the distance between the mucosal surface and the nerve involved as DOI.

Histopathological grading of OSCC

Histopathological grading was first introduced by Broders for squamous cell carcinoma of the lip and was based on the differences in differentiation between tumors [35]. Later, more complex grading systems were suggested by Jakobsson et al. [36], Anneroth et al. [37], and Bryne et al. [38]. These multifactorial systems consider features of the tumor per se (e.g. differentiation), the tumor host interface (invasion patterns), and host reactions (inflammatory response). They influenced formulating the concept of favorable/cohesive and dys- and non-cohesive patterns of invasion in the minimum data sets of the Royal College of Pathologists (United Kingdom) [19,20], to which a dispersed pattern was recently added [10]. These systems should be updated by introducing the feature of myofibroblasts or cancer-associated fibroblasts, which often assessed with the use of immunohistochemistry for alpha smooth muscle actin [39,40].

Curiously, the World Health Organization (WHO) did not endorse such multifactorial systems and paid little attention to minimum data sets or standardized histopathological reporting. The current edition of the Classification of Head and Neck Tumors supports a simple grading system [41] based on the Broders criteria and merely recognizes well-, moderately-, and poorly-differentiated variants of conventional OSCCs, although they acknowledge that “Grading alone does not correlate well

with prognosis” [41]. Many studies indicate minor or no prognostic value of the WHO grading system [42,43]. The data sets of the Royal College of Pathologists (United Kingdom) [9] and sets from Müller et al. [10] would be the sensible alternative.

The dys-/non-cohesive and dispersed invasive patterns defined in the aforementioned sets also likely include tumor budding. Elseragy et al. [44] added tumor budding to the WHO differentiation criteria and showed a better prognostic value than the conventional WHO system in a series of early oral tongue SCC [44]. Further validation in large cohorts of OSCC would be desirable.

A different approach was based on tumor budding and the size of cell nests but was independent of the degree of cell differentiation [45]. Arora et al. assessed the prognostic significance of multiple features, including T stage, tumor grade, tumor budding, tumor thickness, depth of invasion, shape of tumor nests, lymphoid response at the tumor-host interface, and the pattern of invasion, eosinophilic reaction, foreign-body giant cell reaction, lymphovascular invasion, and perineural invasion [46]. They reported that on univariate and multivariate analyses, seven of these were independent variables for predicting lymph node metastasis. In descending order, these were depth of invasion ($P = 0.003$), pattern of invasion ($P = 0.007$), perineural invasion ($P = 0.014$), grade ($P = 0.028$), lymphovascular invasion ($P = 0.038$), lymphoid response ($P = 0.037$), and tumor budding ($P = 0.039$). It was observed that the pattern of invasion scores higher than tumor budding, but the relationship between these features should be clarified.

Whatever that relationship may be, “tumor budding” has become fashionable as a potential prognostic feature in OSCC [47–49]. Such a trend reflects an appealing terminology and the endorsement of the concept of tumor budding also in other cancers [50,51].

Assessing tumor and stromal features to improve risk stratification

Traditional approaches in histopathological grading are centered on the tumor per se (e.g. differentiation, mitotic activity, DOI) rather than stroma and host responses. The multifactorial systems suggested by Jakobsson et al. [36], Anneroth et al. [37], and Bryne et al. [38,52] attempted to make improvements. Currently, the role of the micro-environment in tumor progression spearheads cancer research [53]. The significance of myofibroblasts and cancer-associated fibroblasts was already mentioned above.

Stromal myofibroblasts are innate components of the so-called desmoplastic reaction (desmoplasia) in OSCC [19,20]. Except for myofibroblasts, stromal glycosaminoglycans (GAGs) are also involved in that reaction. Although usually assessed by mucosubstance histochemistry and immunohistochemistry, GAGs can also be studied by immunohistochemistry and visualized to some degree also in routine HE sections (Fig. 2) [19,20]. However, little attention has been paid to the role of GAGs as possible prognosticators in OSCC [54].

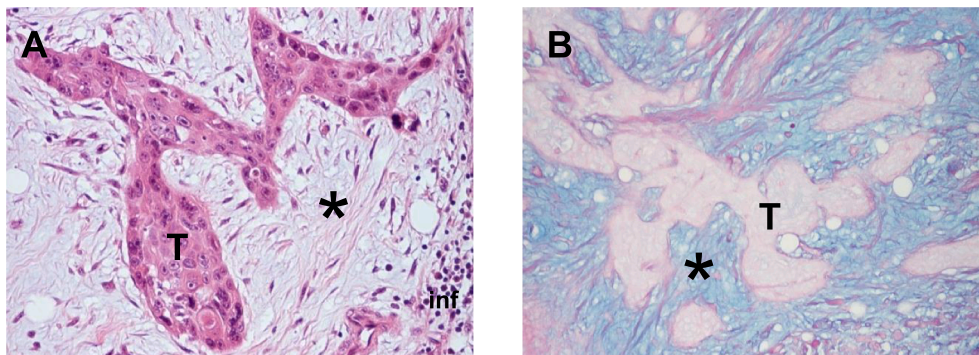


Fig. 2. (A) GAGs (asterisk) in the stroma of SCC (T) (H & E). They are easily distinguished from tumor or the host inflammatory reaction (inf). Modified from (Woolgar and Triantafyllou 2011). (B) Histochemistry for mucosubstances demonstrates the Alcianophilia of GAGs (asterisk); the tumor cell aggregates (T) are unstained.

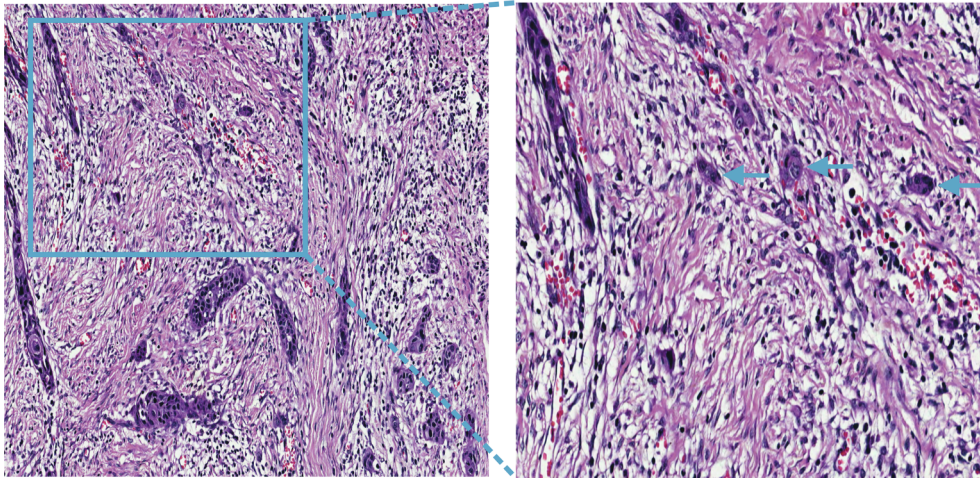


Fig. 3. SCC with stroma-rich tumor. The stroma includes areas of a fibrous appearance intermingled with lymphocytic infiltrates. The infiltrates are associated with loose matrix and they are often located around carcinomatous components of non-cohesive, dispersive, or budding (arrows) growth patterns.

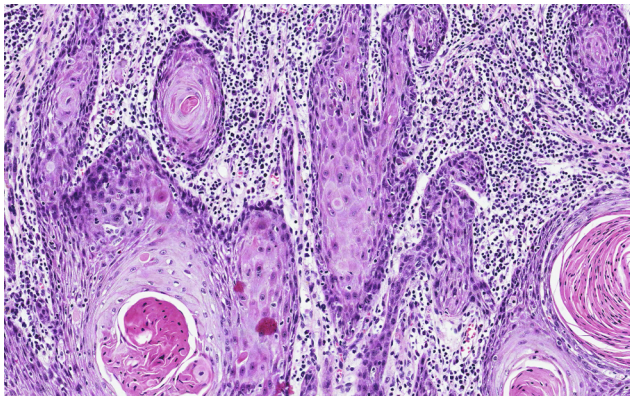


Fig. 4. In comparison with Fig. 3, this SCC shows stroma-poor tumor. The stroma shows widespread lymphocytic infiltration in a largely loose matrix; fibrous areas are inconspicuous.

The so-called immunoscore has been used to characterize various cancers [55,56]. Zhou et al. have recently developed an immune-based prognostic score that includes seven features (such as CD 3 and CD 8) that has significant clinical relevance for survival [57]. Such assessment may be used to identify cases that could benefit from immunotherapy [58]. Endorsing a different approach, Heikkinen et al. suggested that an overall assessment of stromal tumor-infiltrating lymphocytes (TILs) allows risk stratification in early stage oral tongue SCC [59]. This assessment can be easily incorporated in routine histopathology reporting based on HE-stained sections (Figs. 3 and 4). At the same time, recent studies have used immunohistochemistry and reported the significance of different subtypes of lymphocytes and other immune cell components (e.g. dendritic cells) in the prediction of overall survival and disease-free survival [60–64]. Based on the accumulated evidence, recent meta-analyses have identified specific immune biomarkers (e.g. CD57+ and CD163+) for prognostication of OSCC [65,66].

Finally, the tumor-stroma ratio (TSR) was also examined in early-stage oral tongue SCC and may be of useful prognostic significance [67]. Stroma-rich tumors (Fig. 3) are associated with increased recurrence and mortality compared with stroma-poor tumors (Fig. 4) [67]. Again, the assessment of TSR is simple and easily performed on HE-stained slides. A recent meta-analysis indicated the importance of TSR in many cancers [68].

We would like to re-emphasize that the assessment of stromal myofibroblasts, GAGs, TILs, and TSR is cost-effective and can be included in the histopathology report with minimal effort.

Artificial intelligence to improve staging, grading and treatment planning

Treatment planning is a multifactorial process and many factors and parameters with a variable impact should be considered in the decision-making process for management of OSCC. Recently, artificial intelligence and machine-learning tools have been used to analyze factors that could influence the probability of survival, including TNM stage and WHO grade [69]. Regarding OSCC, Bur et al. [70] used machine learning and developed a predictive algorithm that consists of many prognostic factors (including tumor grade) to predict lymph node metastasis in early-stage tumors. Similarly, Kim et al. [71] used many clinicopathologic characteristics (including stage and grade) for deep learning prognostication that may improve prediction of survival after treatment of OSCC. Furthermore, Alabi et al. [72] used machine learning to construct an artificial neural network and also developed a web-based tool to allow for the assessment of several parameters (including stage and grade) to estimate the risk of recurrence in early oral tongue cancer [72].

Insights and perspectives

Possible improvements for TNM staging and WHO grading [15,16,29,30,44] may assist risk stratification of OSCC. The role of the anatomical sub-site should be considered and distinction between early- and advanced-stage OSCCs is important. Prospective studies are necessary. A recent review observes that due to the heterogeneity of methodological approaches, it is impossible to perform a satisfactory meta-analysis for the identification of biomarkers specific for OSCC [73]. Efforts to overcome these difficulties should be undertaken as the identification of biomarkers that allow the screening and identification of individuals who are at risk of developing a primary OSCC or predict relapse after treatment would be a clear way forward. Artificial intelligence has recently shown potential as a promising tool to analyze patient survival based on many factors, including staging and grading. Further research on OSCC should consider application of artificial intelligence in large multi-institutional studies.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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